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A single pacemaker can produce different rates of reentrainment in different overt rhythms

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SUMMARY Using a simple Van der Pol oscillator, we show that periodic events triggered by different states of the oscillator can reentrain at different rates following a phase shift of the Zeitgeber. Such differences can emerge due to waveform distortion during reentrainment, due to masking and due to fitting procedures (e.g. acrophase determination). Therefore, different rates of reentrainment are consistent with single pacemaker models of circadian systems. Likewise, “Fractional Desynchronization” can yield different “ranges of entrainment” in different overt rhythms generated by the same pacemaker.

KEYWORDS reentrainment rate, Van der Pol oscillator, fractional desynchronization, multioscillator models, circadian rhythm.

The complexity of circadian patterning of activity and rest has been widely attributed to a multiplicity of underlying oscillators (Wever 1975; Moore-Ede 1983). Indeed there is anatomical evidence for at least two pacemakers in the case of left–right redundancy, as in, e.g. arthropods and molluscs (Page 1988). Perhaps the splitting of activity rhythms in small mammals also reflects the dual anatomy of the SCN (Daan and Berde 1978; Pickard and Turek 1982; Beersma and Daan 1992). A functionally dissimilar second oscillator is in evidence in cases where a rhythm persists after destruction of the main pacemaker. Such evidence has been provided in rodents for the anticipation of feeding schedules (Stephan 1982), activity under metamphetamine treatment (Honma *et al.* 1987) and visual sensitivity (Terman and Terman 1985).

In other cases, functional multiplicity of oscillators has been claimed in intact systems, on the basis of temporary differences in cycle durations: internal desynchronization in humans (Wever 1975; Kronauer *et al.* 1982), different rates of reentrainment following a zeitgeber phase shift (Moore Ede *et al.* 1977), and different ranges of entrainment (“fractional desynchronization”, Wever 1983; Folkard *et al.* 1983). We have shown earlier that internal desynchronization does not necessarily or likely involve more than one pacemaker (Daan *et al.* 1984). Here we demonstrate that also different rates of reentrainment and different ranges of

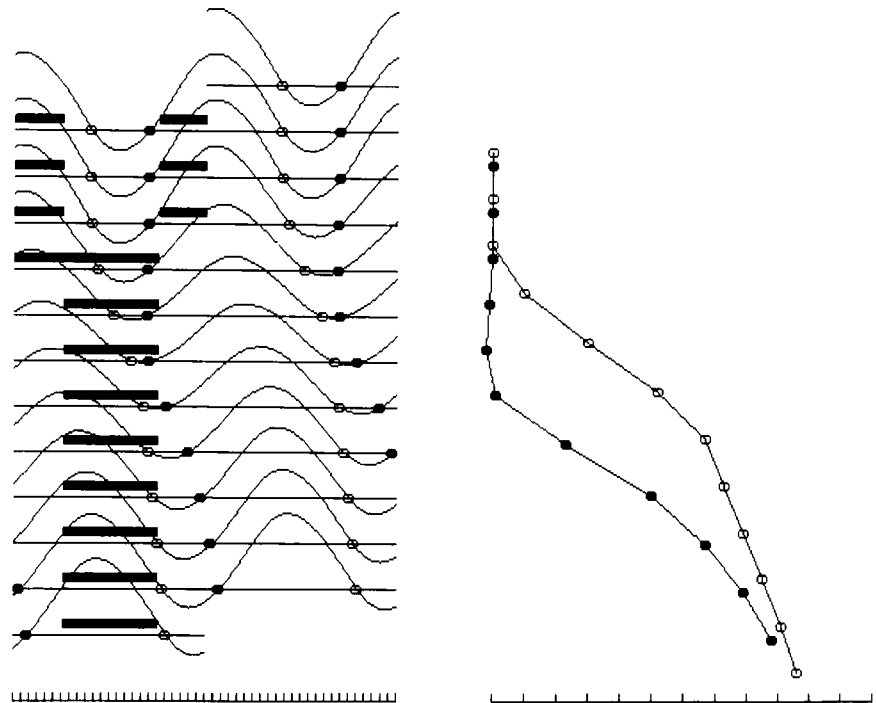
entrainment in Wever’s (1983) protocol may arise from the oscillation of a single pacemaker.

We consider one of the simplest single oscillator models, the Van der Pol oscillator. A similar model was introduced early on as a model of the circadian system by Wever (1963).

$$24^2/(2 \cdot \pi)^2 \cdot d^2y/dt^2 \\ = dB/dt - \mu \cdot 24/(2 \cdot \pi) \cdot (y^2 - 1) \cdot dy/dt - (24/\tau)^2 \cdot y \quad (1)$$

where B = perceived illumination, μ = stiffness, τ = intrinsic period of oscillator (in DD), t = time, y = oscillating variable. Figure 1 (left panel) shows the double-plotted time course of y when the oscillator is ‘exposed’ to an LD 12:12 Zeitgeber. On the fourth day a phase shift of 12 h is introduced in the Zeitgeber. The oscillation now necessarily goes through a series of transients of distorted waveforms before returning to its original form displaced by 12 h. During the transients, phase is no longer uniquely defined. As an example two events (‘phases’) of the oscillation determined by upward and downward crossings of a certain fixed threshold ($y = -1.5$; the amplitude of the oscillation equals 2) have been indicated in Fig. 1A by solid and open symbols, respectively. As the amplitude is temporarily reduced during the transients, the time interval between these “phases” contracts and later diverges again. If pacemaker state at these two “phases” would trigger different physiological or behavioural events, the reentrainment curves for these events would run as indicated in Fig. 1B. Here the ‘phases’ are plotted relative to their initial

Figure 1. (A) (left) Simulation of the Van der Pol oscillator model in an LD 12:12 cycle. B alternates between 0 in D (black bars) and 1 in L. The oscillation is double plotted, with the LD cycle indicated only in the left half. Horizontal lines indicate the fixed value $y = -1.5$. Dots mark the upward crossing, circles the downward crossing of this line. After three cycles of stable entrainment a 12 h phase shift of the LD cycle is introduced. Ticks on the bottom line mark 1 h intervals. (B) (right) Exploded view of the phase shifts in the two events relative to their position before the phase shift. Ticks on the bottom line mark 1 h intervals.



temporal position. Clearly, the distortion of even such a simple, near-harmonic oscillation may cause major incongruencies in the reentrainment rate of nonoscillatory events attached to it.

A second cause of differential reentrainment rates is *masking* (see also Minors and Waterhouse, 1988). To illustrate the consequence of masking we have used the same oscillation as in Fig. 1A, and indicated the phases of the upward threshold crossing again by solid dots in Fig. 2A. We assumed that the pacemaker creates an oscillation shifted downward by masking over 0.8 units during light and shifted upward over 0.8 units during dark. The resulting threshold crossings are shown by open symbols. The masked rhythm as indicated by this 'phase' shifts more rapidly and thus would suggest a greater rate of reentrainment (Fig. 2B), even though generated by the same oscillator.

The effects of differential attachment to the pacemaker and differential masking were shown for single events where there is no uncertainty in the determination of the event. For physiological variables under continuous control of the pacemaker state variable there is an additional effect inherent in standard procedures of phase estimation. For instance, acrophase determination during transients, when waveform as well as period of the pacemaker differ from those under stable entrainment, must introduce a further bias. The size of this bias depends on how the pacemaker controls the overt rhythm. We thus should expect that rates of reentrainment as deduced from acrophases of different physiological variables differ due to application of the fitting procedure.

There are three reasons why different rates of reentrainment should not be treated as suggestive of

different underlying oscillators. All three derive from the waveform distortion during the transients. There are other experimental protocols in which there is no stable entrainment. Wever (1983) introduced the "Fractional Desynchronization" protocol. In this protocol, human subjects are exposed to a sequence of zeitgeber cycles, with constant increments or decrements in cycle duration. Typically, these cycles would consist of alternating bright and dim light of equal duration, while the cycle length increased from 26 h to 30 h or decreased from 24 h to 20 h in steps of 5 or 10 min per cycle. Wever (1983) claimed that this protocol allows one to differentiate between the ranges of entrainment of different overt physiological rhythms. Different functions would break away from the light cycle on different days. The cycle length (T) at which this happened would define the upper or lower end of the range of entrainment, for increasing and decreasing T -protocols, respectively. Folkard *et al.* (1983) interpreted different boundaries of the entrainment range as suggestive of different underlying oscillators. We argue that with a continuously changing zeitgeber, there is never stable entrainment, and hence the range of entrainment can not be properly assessed. The transient nature of all the phase relationships established leads to wave form distortion with the same problems as in a reentrainment protocol. For the purpose of illustration, we have in Fig. 3 subjected our Van der Pol oscillator to an LD zeitgeber of increasing T . The oscillator initially shows a gradual change of phase relationship (dots, indicating the minima) and then drifts into relative coordination. Adding a slight masking factor to the y -value causes the phase reference to behave completely differently (circles; here we used downward crossings of $y = -1.5$, to avoid initial superposition of the symbols).

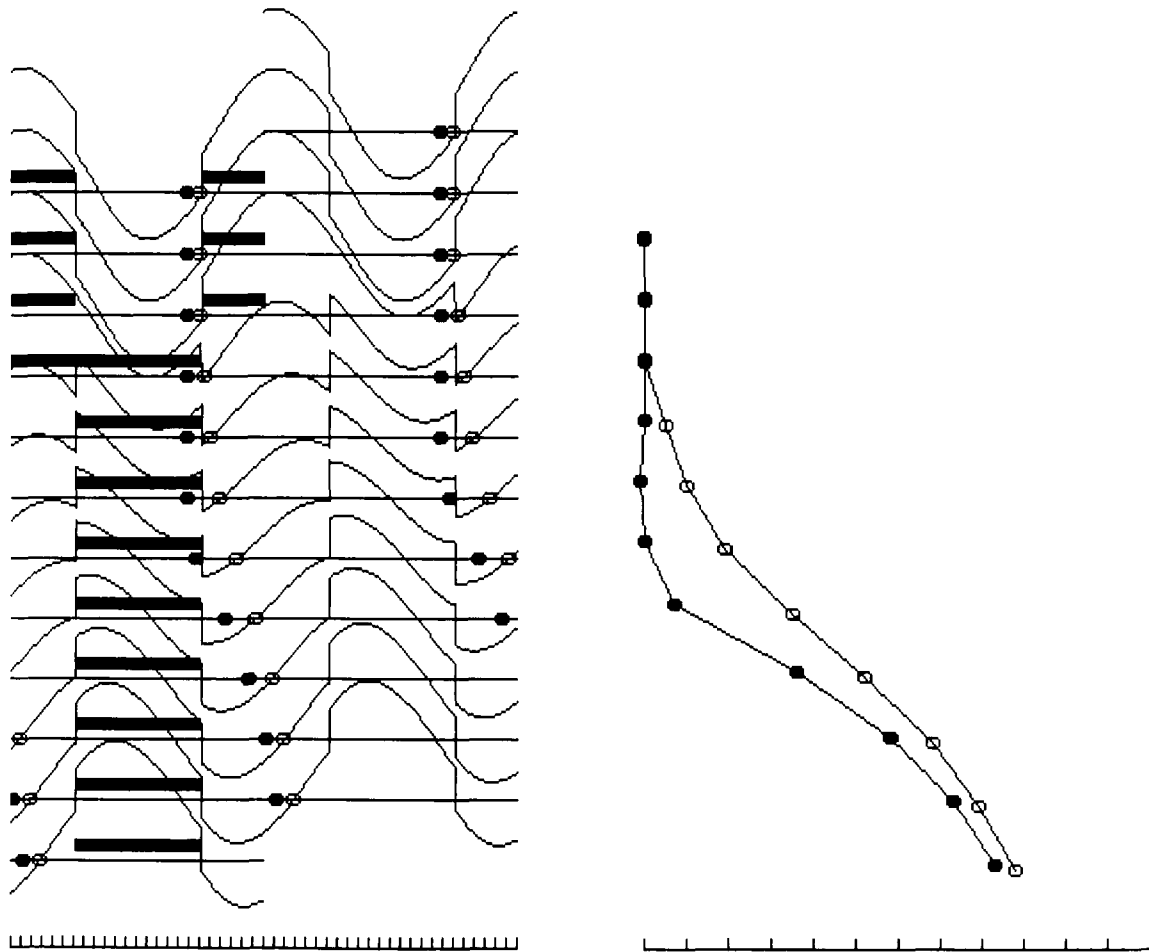


Figure 2. (A) (left) Simulation of the Van der Pol oscillator model as in Fig. 1, now with masking introduced by adding 0.8 units to y during D, and subtracting 0.8 units during L. Dots: upward crossings of $y = -1.5$, taken from Fig. 1 (without masking). Circles: upward crossings of $y = -1.5$ with masking. (B) (right) Exploded view of the phase shifts in the masked and the unmasked events relative to their position before the phase shift.

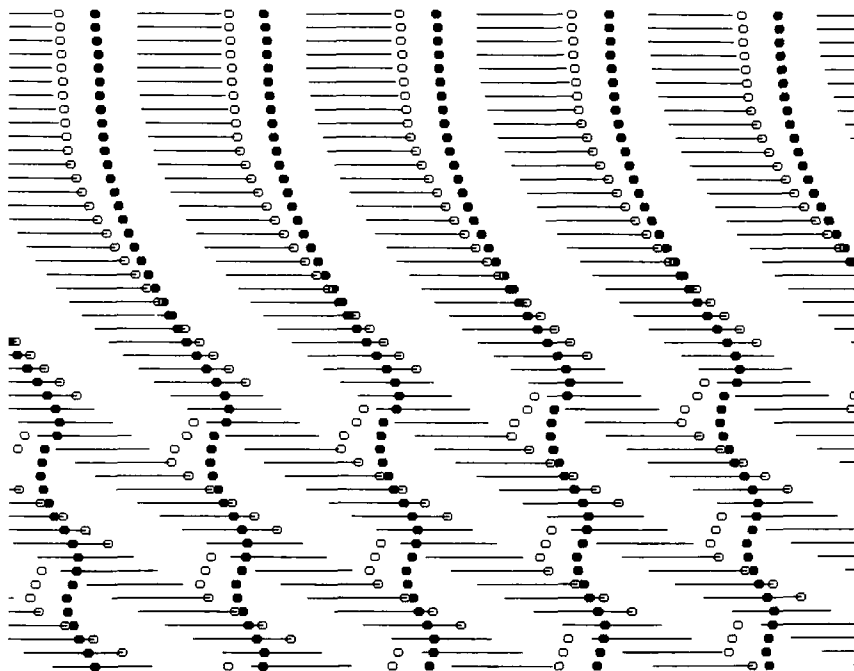


Figure 3. Quintuple plot of events in the oscillator under a fractional desynchronization protocol. Lines indicate dark episodes. Dots: minima in the unmasked oscillation. Circles: downward crossings of $y = -1.5$ in the masked oscillation.

There are protracted episodes during which the masked oscillation closely follows the LD-cycle, followed by sudden phase jumps. Even though both functions are generated by the same oscillator, they would be interpreted in the fractional desynchronization protocol as being generated by two oscillators with different ranges of entrainment.

In summary, differences in transient behaviour do not necessarily point to differences in the generating mechanism of oscillations. This holds not only for different physiological and behavioural functions, but also for comparison between individuals. For instance, the slow rate of reentrainment of mice selected for aggressive behaviour (Benus *et al.*, 1988) is not necessarily the consequence of changes at the level of the circadian pacemaker. Since neither transient behaviour nor stable entrained behaviour in the presence of a zeitgeber can thus differentiate between single and multiple oscillators, we conclude that only multiple frequencies in a freerunning system and the persistence of a circadian oscillation following destruction of a known pacemaker can force the conclusion of multiple oscillators.

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